CLAIMS

1. A crystal of a protein complex between granulocyte colony-stimulating factor (G-CSF) and the G-CSF binding region (CRH-G-CSF-R) of the granulocyte colony-stimulating factor receptor (G-CSF-R).

2. A crystal of a protein complex according to claim 1 wherein G-CSF and CRH-G-CSF-R are derived from a mammal or mammals.

3. A crystal of a protein complex according to claim 2 wherein G-CSF comprises a human-type sequence shown in SEQ ID NO: 1, and CRH-G-CSF-R comprises a mouse-type sequence shown in SEQ ID NO: 2.

4. A crystal according to any one of claims 1 to 3 wherein the crystal has the tetragonal space group symmetry $I4_122$.

5. A crystal according to claim 4 wherein the unit cell parameters of the crystal are a=b=125±10 Å and c=373±10 Å.

6. A crystal according to any one of claims 1 to 3 wherein the crystal has the tetragonal space group symmetry $P4_32_12$.

7. A crystal according to claim 6 wherein the unit cell parameters of the crystal are a=b=126±10 Å and c=373±10 Å.

8. A crystal according to any one of claims 1 to 7 wherein stoichiometrically equivalent quantities of G-CSF and CRH-G-CSF-R bind together to form the complex.

9. A crystal according to any one of claims 1 to 5 wherein stoichiometrically equivalent quantities of G-CSF and CRH-G-CSF-R bind together to form the complex and two molecules of the complex exist in a crystallographic asymmetric unit.

10. A crystal according to any one of claims 1 to 3, 6, and 7 wherein stoichiometrically equivalent quantities of G-CSF and CRH-G-CSF-R bind together to form the complex and four molecules of the complex exist in a crystallographic asymmetric unit.

11. A crystal according to any one of claims 1 to 10 wherein the regions forming the complex between G-CSF and CRH-G-CSF-R are characterized by all or part of amino acid residues S13, L16, K17, E20, Q21, R23, K24, L109, D110, D113, T116, T117, Q120, E123, E124 and amino acid residues adjacent thereto in the amino acid sequence of human-type G-CSF shown in SEQ ID NO: 1.

12. A crystal according to any one of claims 1 to 10 wherein the regions forming the complex between G-CSF and CRH-G-CSF-R are characterized by all or part of amino acid residues N20, S45, R46, R72, K73, L75, L76, L77, Y78, Q79, Y80, D102, M104, D105, Y143, M144, E145, R193, S195, L196

and amino acid residues adjacent thereto in the amino acid sequence of mouse-type CRH-G-CSF-R shown in SEQ ID NO: 2.

13. A crystal according to any one of claims 1 to 10 wherein the regions forming the associate of the complex between G-CSF and CRH-G-CSF-R are characterized by all or part of amino acid residues G5, P6, A7, S8, S9, L10, P11, Q12, L125 and amino acid residues adjacent thereto in the amino acid sequence of human-type G-CSF shown in SEQ ID NO: 1.

14. A crystal according to any one of claims 1 to 10 wherein the regions forming the associate of the complex between G-CSF and CRH-G-CSF-R are characterized by all or part of amino acid residues W161, L163, V164, F165, H166, L167, P168, and K171 and amino acid residues adjacent thereto in the amino acid sequence of mouse-type CRH-G-CSF-R shown in SEQ ID NO: 2.

15. A crystal according to any one of claims 1 to 10 wherein amino acid residues exposed to the solvent region on the side of the binding surface formed by the associate of the complex between G-CSF and CRH-G-CSF-R were characterized by all or part of amino acid residues Y3 to L14, R46 to Y51, G92 to V106, E145 to E147, H166 to S169, S194 to G198 and amino acid residues adjacent thereto in the amino acid sequence of mouse-type CRH-G-CSF-R shown in SEQ ID NO: 2.

16. Three-dimensional structure coordinates of a complex formed by G-CSF and CRH-G-CSF-R for use in identifying, searching for, evaluating, or designing variants, agonists, or antagonists of G-CSF.

17. Three-dimensional structure coordinates according to claim 16 wherein the three-dimensional structure coordinates are those shown in Table 1.

18. Three-dimensional structure coordinates according to claim 16 wherein the three-dimensional structure coordinates are those of a complex between G-CSF derived from a species other than human comprising a sequence having 20% or more homology to the amino acid sequence of human-type G-CSF and CRH-G-CSF-R derived from a species other than mouse comprising a sequence having 20% or more homology to the amino acid sequence of mouse-type CRH-G-CSF-R determined by a molecular replacement method or using a homology model.

19. Three-dimensional structure coordinates according to claim 18 wherein the three-dimensional structure coordinates are those shown in Table 6.

20. A computer storage medium storing all or part of the three-dimensional structure coordinates according to any one of claims 16 to 19 for use in identifying, searching for, evaluating, or designing a variant, agonist, or antagonist of G-CSF.

21. Use of all or part of the three-dimensional structure coordinates according to any one of claims 16 to 19 or the computer storage medium according to claim 20 for identifying, searching for, evaluating, or designing a variant, agonist, or antagonist of G-CSF.

22. Use of claim 21 characterized in that the three-dimensional structure coordinates are those of amino acid residues shown in Tables 2 to 5 or amino acid residues adjacent thereto.

23. A method of identifying, searching for, evaluating, or designing a G-CSF variant which has biological activities equal or superior to those of native G-CSF and in which one or more amino acid residues have been substituted, deleted, inserted, or chemically modified, the method being characterized in that it uses all or part of the three-dimensional coordinates according to any one of claims 16 to 19 or the computer storage medium according to claim 20.

24. A method of identifying, searching for, evaluating, or designing a G-CSF variant which has activity as an antagonist and in which one or more amino acid residues have been substituted, deleted, inserted, or chemically modified, the method being characterized in that it uses all or part of the three-dimensional coordinates according to any one of claims 16 to 19 or the computer

storage medium according to claim 20.

25. A method according to claim 23 or 24 wherein the variant is substitution, deletion, insertion, or chemical modification of one or more of amino acid residues G5, P6, A7, S8, S9, L10, P11, Q12, S13, L16, K17, E20, Q21, R23, K24, L109, D110, D113, T116, T117, Q120, E123, E124, L125 and amino acid residues adjacent thereto in human-type G-CSF shown in SEQ ID NO: 1.

26. A G-CSF variant in which one or more of amino acid residues G5, P6, A7, S8, S9, L10, P11, Q12, S13, L16, K17, E20, Q21, R23, K24, L109, D110, D113, T116, T117, Q120, E123, E124, L125 and amino acid residues adjacent thereto have been substituted, deleted, inserted, or chemically modified in human-type G-CSF shown in SEQ ID NO: 1.

27. A method of identifying, searching for, evaluating, or designing a G-CSF agonist, the method being characterized in that it uses all or part of the three-dimensional structure coordinates according to claims 16 to 19 or the computer storage medium according to claim 20.

28. A method according to claim 27 wherein it particularly uses three-dimensional coordinates of the positions corresponding to amino acid residues Y3 to L14, R46 to Y51, G92 to V106, E145 to E147, H166 to S169, S194 to G198 and amino acid residues adjacent thereto among those shown in Table 1 or 6.

29. A method according to claim 27 or 28 wherein the agonist binds to CRH-G-CSF-R and thereby provides spatial positions of CRH-G-CSF-R substantially identical to those of the CRH-G-CSF-R in the associate of the complex between CHR-G-CSF-R and G-CSF and wherein the agonist binds to CRH-G-CSF-R at two or more sites.

30. A compound which is an agonist of G-CSF and is obtained using a method of drug design according to any one of claims 27 to 29.

31. A compound according to claim 30 wherein the agonist of G-CSF is a natural or synthetic compound.

32. A method of identifying, searching for, evaluating, or designing an antagonist of G-CSF, the method being characterized in that it uses all or part of the three-dimensional coordinates according to any one of claims 16 to 19 or the computer storage medium according to claim 20.

33. A method according to claim 32 wherein the antagonist is a compound which binds to G-CSF and inhibits binding of G-CSF to G-CSF-R.

34. A method according to claim 32 wherein the antagonist is a compound which binds to CRH-G-CSF-R and inhibits binding of G-CSF to G-CSF-R.

35. A method according to claim 32 wherein the antagonist is a compound which binds to the complex between

G-CSF and G-CSF-R and inhibits normal binding between G-CSF and G-CSF-R.

36. A compound which is an antagonist of G-CSF and is obtained using a method according to any one of claims 32 to 35.

37. A compound according to claim 36 wherein the antagonist of G-CSF is a natural or synthetic compound.

38. Use of all or part of the three-dimensional structure coordinates according to any one of claims 16 to 19 or the computer storage medium according to claim 20 in crystallography using the technique of molecular replacement.